

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions, and listings, of claims in the application. Please amend claims 5-12, 14, 18, 20, 21, 23, 26, 28, 29, 31, 34, 36, 38, 40, 42, 44, 46, 48, 50-54, 56, 58, 62-65, and 72-75 as follows.

Listing of the Claims

Claim 1 (Original): A peptide comprising an amino acid sequence having a cleavage site specific for an enzyme having a proteolytic activity of human kallikrein 2 (hK2), wherein the peptide comprises the sequence G-K-A-X₁-X₂-X₃, wherein at least one of X₁, X₂, and X₃ is arginine, and wherein the other two amino acid residues at X₁, X₂, and X₃ are each any amino acid residue.

Claim 2 (Original): The peptide of claim 1, further comprising a nitrotyrosine quencher at the amino terminus of the peptide.

Claim 3 (Original): The peptide of claim 1, further comprising K(ABZ) at the carboxy terminus of the peptide.

Claim 4 (Original): The peptide of claim 1, further comprising a nitrotyrosine quencher at the amino terminus of the peptide and K(ABZ) at the carboxy terminus of the peptide.

Claim 5 (Currently Amended): The peptide of ~~any one of claims 1-4~~ claim 4, which comprises the sequence NO₂-Y-G-K-A-X₁-X₂-X₃-Dap-K(ABZ).

Claim 6 (Currently Amended): The peptide of ~~any one of claims 1-5~~ claim 1, wherein the peptide is cleaved by hK2 after the amino acid residue X₁.

Claim 7 (Currently Amended): The peptide of ~~any one of claims 1-5~~ claim 1, wherein the peptide is cleaved by hK2 after the amino acid residue X₂.

Claim 8 (Currently Amended): The peptide of ~~any one of claims 1-5~~ claim 1, wherein the peptide is cleaved by hK2 after the amino acid residue X₃.

Claim 9 (Currently Amended): The peptide of ~~any one of claims 1-5~~ claim 1, wherein the peptide is cleaved by hK2 after the amino acid residue X₂ and/or after the amino acid residue X₃.

Claim 10 (Currently Amended): The peptide of ~~any one of claims 1-9~~ claim 1, wherein the peptide is cleaved by hK2 after an arginine (R) residue.

Claim 11 (Currently Amended): The peptide of ~~any one of claims 1-10~~ claim 1, wherein the peptide comprises the amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32.

Claim 12 (Currently Amended): The peptide of ~~any one of claims 1-11~~ claim 1, further comprising a capping group attached to the N-terminus of the peptide, wherein the capping group inhibits endopeptidase activity on the peptide.

Claim 13 (Original): The peptide of claim 12, wherein the capping group is selected from the group consisting of acetyl, morpholinocarbonyl, benzyloxycarbonyl, glutaryl and succinyl substituents.

Claim 14 (Currently Amended): The peptide of ~~any one of claims 1-13~~ claim 1, further comprising an added substituent which renders the peptide water-soluble.

Claim 15 (Original): The peptide of claim 14, wherein the added substituent is a polymer.

Claim 16 (Original): The peptide of claim 15, wherein the polymer is selected from the group consisting of polylysine, polyethylene glycol (PEG), and a polysaccharide.

Claim 17 (Original): The peptide of claim 16, wherein the polysaccharide is selected from the group consisting of modified or unmodified dextran, cyclodextrin, and starch.

Claim 18 (Currently Amended): The peptide of ~~any one of claims 1-17~~ claim 1, further comprising an antibody attached to the amino terminus of the peptide.

Claim 19 (Original): A peptide composition comprising a plurality of peptides, each peptide comprising an amino acid sequence having a cleavage site specific for an enzyme having a proteolytic activity of human kallikrein 2 (hK2), wherein each peptide comprises the sequence G-K-A-X₁-X₂-X₃, wherein at least one of X₁, X₂, and X₃ is arginine, and wherein the other two amino acid residues at X₁, X₂, and X₃ are each any amino acid residue.

Claim 20 (Currently Amended): A polynucleotide encoding the peptide of ~~any one of claims 1-14~~ claim 1.

Claim 21 (Currently Amended): A composition comprising a prodrug, the prodrug comprising
a therapeutically active drug; and
a peptide of ~~any one of claims 1-19~~ claim 1,
wherein the peptide is linked to the therapeutically active drug to inhibit the therapeutic activity of the drug, and wherein the therapeutically active drug is cleaved from the peptide upon proteolysis by an enzyme having a proteolytic activity of human kallikrein 2 (hK2).

Claim 22 (Original): The composition of claim 21, wherein the peptide is linked directly to the therapeutic drug.

Claim 23 (Currently Amended): The composition of ~~any one of claims 21-22~~ claim 22, wherein the peptide is linked directly to a primary amine group on the drug.

Claim 24 (Original): The composition of claim 21, wherein the peptide is linked to the therapeutic drug via a linker.

Claim 25 (Original): The composition of claim 24, wherein the linker is an amino acid sequence.

Claim 26 (Currently Amended): The composition of ~~any one of claims 24-25~~ claim 25, wherein the linker comprises a leucine residue.

Claim 27 (Original): The composition of claim 24, wherein the linker is selected from the group consisting of unsubstituted or alkyl-, aryl-, halo-, alkoxy-, alkenyl-, amido- or amino-substituted $\text{CO}-(\text{CH}=\text{CH})_{n1}-(\text{CH}_2)_{n2}-\text{Ar}-\text{NH}_2$, $\text{CO}-(\text{CH}_2)_{n2}-(\text{CH}=\text{CH})_{n1}-\text{Ar}-\text{NH}_2$, $\text{CO}-(\text{CH}_2)_{n2}-(\text{CH}=\text{CH})_{n1}-\text{CO}-\text{NH}-\text{Ar}-\text{NH}_2$, $\text{CO}-(\text{CH}=\text{CH})_{n1}-(\text{CH}_2)_{n2}-\text{CO}-\text{NH}-\text{Ar}-\text{NH}_2$, $\text{CO}-(\text{CH}_2)_{n3}-\text{NH}_2$, and $\text{CO}-(\text{CH}_2)_{n3}-\text{NH}-\text{CO}-\text{CH}(\text{R}_4)-\text{NH}_2$, wherein $n1$ and $n2$ are from 0 to 5, $n3$ is from 0 to 15, Ar is any substituted or unsubstituted aryl group, attachment of NH_2 to Ar is in a ortho, meta or para position with respect to the remainder of the linker, and R_4 is any naturally occurring amino acid side chain.

Claim 28 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug inhibits a SERCA pump.

Claim 29 (Currently Amended): The composition of ~~any one of claims 21-28~~ claim 21, wherein the therapeutically active drug is selected from the group of primary amine containing thapsigargin or thapsigargin derivatives.

Claim 30 (Original): The composition of claim 29, wherein the thapsigargin derivative is 8-O-(12-[L-leucinoylamino]dodecanoyl)-8-O-debutanoylthapsigargin (L12ADT).

Claim 31 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug intercalates into a polynucleotide.

Claim 32 (Original): The composition of claim 31, wherein the therapeutically active drug is an anthracycline.

Claim 33 (Original): The composition of claim 32, wherein the anthracycline is selected from the group consisting of doxorubicin, daunorubicin, epirubicin, and idarubicin.

Claim 34 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug is a taxane.

Claim 35 (Original): The composition of claim 34, wherein the taxane is selected from the group consisting of paclitaxel and docetaxel.

Claim 36 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug is a vinca alkaloid.

Claim 37 (Original): The composition of claim 36, wherein the vinca alkaloid is selected from the group consisting of vincristine, vinblastine, and etoposide.

Claim 38 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug is an antiandrogen.

Claim 39 (Original): The composition of claim 38, wherein the antiandrogen is selected from the group consisting of bicalutamide, flutamide, nilutamide, and cyproterone acetate.

Claim 40 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug is an antifolate.

Claim 41 (Original): The composition of claim 40, wherein the antifolate is methotrexate.

Claim 42 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug is a nucleoside analog.

Claim 43 (Original): The composition of claim 42, wherein the nucleoside analog is selected from the group consisting of 5-Fluorouracil, gemcitabine, and 5-azacytidine.

Claim 44 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug is a topoisomerase inhibitor.

Claim 45 (Original): The composition of claim 44, wherein the topoisomerase inhibitor is selected from the group consisting of Topotecan and irinotecan.

Claim 46 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug is an alkylating agent.

Claim 47 (Original): The composition of claim 46, wherein the alkylating agent is selected from the group consisting of cyclophosphamide, Cisplatinum, carboplatinum, and ifosfamide.

Claim 48 (Currently Amended): The composition of ~~any one of claims 21-27~~ claim 21, wherein the therapeutically active drug is a targeted radiation sensitizer.

Claim 49 (Original): The composition of claim 48, wherein the targeted radiation sensitizer is selected from the group consisting of 5-fluorouracil, gemcitabine, topoisomerase inhibitors, and cisplatinum.

Claim 50 (Currently Amended): The composition of any ~~one of claims 21-49~~ claim 21, wherein the therapeutically active drug has an IC_{50} toward ER Ca^{2+} -ATPase of at most 500 nM.

Claim 51 (Currently Amended): The composition of any ~~one of claims 21-49~~ claim 21, wherein the therapeutically active drug has an IC_{50} toward ER Ca^{2+} -ATPase of at most 50 nM.

Claim 52 (Currently Amended): The composition of any ~~one of claims 21-49~~ claim 21, wherein the therapeutically active drug has an LC_{50} toward hK2-producing tissue of at most 20 μM .

Claim 53 (Currently Amended): The composition of any ~~one of claims 21-49~~ claim 21, wherein the therapeutically active drug has an LC_{50} toward hK2-producing tissue of less than or equal to 2.0 μM .

Claim 54 (Currently Amended): A method of producing a prodrug, the method comprising the step of linking

a therapeutically active drug and

a peptide of any ~~one of claims 1-19~~ claim 1,

wherein the linking of the peptide to the drug inhibits the therapeutic activity of the drug.

Claim 55 (): The method of claim 54, wherein the therapeutically active drug has a primary amine.

Claim 56 (Currently Amended): The method of any ~~one of claims 54-55~~ claim 54, wherein the prodrug contains a linker between the peptide and the drug.

Claim 57 (Original): The method of claim 56, wherein the linker comprises leucine.

Claim 58 (Currently Amended): A method of treating an hK2-producing cell proliferative disorder, the method comprising administering the composition of ~~any one of claims 21-53~~ claim 21 in a therapeutically effective amount to a subject having the cell proliferative disorder.

Claim 59 (Original): The method of claim 58, wherein the disorder is benign.

Claim 60 (Original): The method of claim 58, wherein the disorder is malignant.

Claim 61 (Original): The method of claim 60, wherein the malignant disorder is prostate cancer.

Claim 61 (Original): The method of claim 60, wherein the malignant disorder is breast cancer.

Claim 62 (Currently Amended): The method of ~~any one of claims 58-61~~ claim 58, wherein the composition is administered as a single dose comprising at least about 7 mg/kg peptide.

Claim 63 (Currently Amended): The method of ~~any one of claims 58-61~~ claim 58, wherein the composition is administered as a single dose comprising at least about 17.5 mg/kg peptide.

Claim 64 (Currently Amended): The method of ~~any one of claims 58-61~~ claim 58, wherein the composition is administered in doses of at least about 7 mg/kg peptide per day for at least 4 days.

Claim 65 (Currently Amended): A method of detecting human kallikrein 2-producing tissue, the method comprising:

contacting the tissue with a composition comprising

a detectably labeled peptide of ~~any one of claims 1-19~~ claim 1 for a period of time sufficient to allow cleavage of the peptide; and

detecting the detectable label.

Claim 66 (Original): The method of claim 65, wherein the detectable label is a fluorescent label.

Claim 67 (Original): The method of claim 66, wherein the fluorescent label is selected from the group consisting of 7-amino-4-methyl coumarin, 7-amino-4-trifluoromethyl coumarin, rhodamine 110, and 6-aminoquinoline.

Claim 68 (Original): The method of claim 65, wherein the detectable label is a radioactive label.

Claim 69 (Original): The method of claim 68, wherein the radioactive label is selected from the group consisting of tritium, carbon-14, and iodine-125.

Claim 70 (Original): The method of claim 65, wherein the detectable label is a chromophoric label.

Claim 71 (Original): The method of claim 65, wherein the detectable label is a chemiluminescent label.

Claim 72 (Currently Amended): A method of selecting a human kallikrein 2 (hK2) activatable prodrug wherein the prodrug is substantially specific for target tissue comprising hK2-producing cells, the method comprising:

- a) linking a peptide of any one of ~~claims 1-19~~ claim 1 to a therapeutic drug to produce a peptide-drug composition;
- b) contacting the composition with cells of the target tissue;
- c) contacting the composition with cells of a non-target tissue; and
selecting complexes that are substantially toxic towards target tissue cells, but which are not substantially toxic towards non-target tissue cells.

Claim 73 (Currently Amended): A method of determining the activity of hK2 in a sample containing hK2, the method comprising:

- a) contacting the sample with a composition comprising a detectably labeled peptide of any one of ~~claims 1-19~~ claim 1 for a period of time sufficient to allow cleavage of the peptide;
- b) detecting the detectable label to yield a detection level;
- c) comparing the detection level with a detection level obtained from contacting the detectably labeled peptide with a standard hK2 sample.

Claim 74 (Currently Amended): A method of imaging hK2-producing tissue, the method comprising:

- a) administering a peptide of ~~any one of claims 1-19~~ claim 1 linked to a lipophilic imaging label to a subject having or suspected of having an hK2 producing associated cell-proliferative disorder;
- b) allowing a sufficient period of time to pass to allow cleavage of the peptide by hK2 and to allow clearance of uncleaved peptide from the subject to provide a reliable imaging of the imaging label; and
- c) imaging the subject.

Claim 75 (Currently Amended): A method of identifying a peptide sequence which can be a substrate for hK2 comprising

- a) incubating a random peptide library comprising the peptides of ~~any one of claims 1-19~~ claim 1 with hK2;
 - b) detecting a peptide which is cleaved by hK2; and
 - c) determining the sequence of the cleaved peptide,
- wherein the peptides comprise a label which is detectable only after cleavage by hK2.